

PATENT COOPERATION TREATY

PCT

**NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

PHARMACIA & UPJOHN S.P.A.
Via le Pasteur, 10
I-20014 Nerviano
ITALIE

Date of mailing (day/month/year) 13 March 2000 (13.03.00)	
Applicant's or agent's file reference FC 861/5	IMPORTANT NOTIFICATION
International application No. PCT/EP00/00745	International filing date (day/month/year) 31 January 2000 (31.01.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 25 February 1999 (25.02.99)
Applicant PHARMACIA & UPJOHN S.P.A. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
25 Febr 1999 (25.02.99)	9904387.9	GB	01 Marc 2000 (01.03.00)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer S. De Michiel
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

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**NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES**

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 31 August 2000 (31.08.00)		
Applicant's or agent's file reference FC 861/5	IMPORTANT NOTICE	
International application No. PCT/EP00/00745	International filing date (day/month/year) 31 January 2000 (31.01.00)	Priority date (day/month/year) 25 February 1999 (25.02.99)
Applicant PHARMACIA & UPJOHN S.P.A. et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
AE, AL, AM, AP, AT, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EA, EE, EP, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 31 August 2000 (31.08.00) under No. WO 00/50032

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>J. Zahra</p> <p>Telephone No. (41-22) 338.83.38</p>
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PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 23 October 2000 (23.10.00)	in its capacity as elected Office
International application No. PCT/EP00/00745	Applicant's or agent's file reference FC 861/5
International filing date (day/month/year) 31 January 2000 (31.01.00)	Priority date (day/month/year) 25 February 1999 (25.02.99)
Applicant GERONI, Cristina et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

 15 September 2000 (15.09.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer R. E. Stoffel Telephone No.: (41-22) 338.83.38
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INTERNATIONAL SEARCH REPORT

Int'l. Appl. No.

PCT/EP 00/00745

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/396 A61K31/351 A61P35/00 A61K31/352
 //((A61K31/396, 31:352), (A61K31/396, 31:351), (A61K31/352, 31:351),
 (A61K31/351, 31:351))

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 48503 A (CARUSO MICHELE ; GERONI CRISTINA (IT); PHARMACIA & UPJOHN SPA (IT);) 30 September 1999 (1999-09-30) claims 1-7	1-9
Y	EDE R JP ET AL: "Sequence effect of irinotecan (CPT-11) and topoisomerase II inhibitors in vivo" CANCER CHEMOTHERAPY AND PHARMACOLOGY, DE, SPRINGER VERLAG, BERLIN, vol. 42, no. 4, 1998, pages 327-335, XP002112007 ISSN: 0344-5704 abstract page 334	1-9

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

12 May 2000

Date of mailing of the international search report

22/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenttaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

Inte	Final Application No
PCT/EP 00/00745	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 532 218 A (BARGIOTTI ALBERTO ET AL) 2 July 1996 (1996-07-02) cited in the application claims 1,6,10 —	1-9
Y	US 5 496 808 A (BARGIOTTI ALBERTO ET AL) 5 March 1996 (1996-03-05) cited in the application claims 1,2,29 —	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Jpn Application No

PCT/EP 00/00745

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9948503	A 30-09-1999	AU 3331499	A	18-10-1999
US 5532218	A 02-07-1996	AT 157369	T	15-09-1997
		AU 676625	B	13-03-1997
		AU 1066095	A	03-07-1995
		CA 2154890	A	22-06-1995
		CN 1117734	A, B	28-02-1996
		DE 69405214	D	02-10-1997
		DE 69405214	T	29-01-1998
		DK 683788	T	27-10-1997
		WO 9516695	A	22-06-1995
		EP 0683788	A	29-11-1995
		ES 2107294	T	16-11-1997
		FI 953784	A	09-08-1995
		GR 3025266	T	27-02-1998
		HU 73172	A	28-06-1996
		IL 111725	A	15-07-1998
		JP 8506835	T	23-07-1996
		NO 953163	A	02-10-1995
		NZ 276401	A	24-10-1997
		PL 310177	A	27-11-1995
		ZA 9409701	A	12-12-1995
US 5496808	A 05-03-1996	AT 134376	T	15-03-1996
		AU 661012	B	13-07-1995
		AU 2229492	A	11-02-1993
		CA 2112818	A	21-01-1993
		CN 1069981	A, B	17-03-1993
		CZ 9400024	A	13-07-1994
		DE 69208400	D	28-03-1996
		DE 69208400	T	27-06-1996
		DK 521458	T	18-03-1996
		WO 9301201	A	21-01-1993
		EP 0521458	A	07-01-1993
		FI 940011	A	03-01-1994
		GR 3019429	T	30-06-1996
		HK 1006460	A	26-02-1999
		HU 70480	A	30-10-1995
		IE 76921	B	05-11-1997
		IL 102409	A	08-12-1995
		JP 6508841	T	06-10-1994
		MX 9203928	A	01-04-1993
		NO 940026	A	16-02-1994
		NZ 243450	A	25-11-1993
		ZA 9204971	A	31-03-1993

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FC 861/5	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/00745	International filing date (day/month/year) 31/01/2000	Priority date (day/month/year) 25/02/1999	
International Patent Classification (IPC) or national classification and IPC A61K31/396			
Applicant PHARMACIA & UPJOHN S.P.A.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 15/09/2000	Date of completion of this report 29.05.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrera, S Telephone No. +49 89 2399 8464



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/00745

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-6 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/00745

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-9
	No:	Claims
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-9
Industrial applicability (IA)	Yes:	Claims 1-6
	No:	Claims

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/00745

Section V

1. Reference is made to the following documents:

D1: US-A-5 532 218 (BARGIOTTI ALBERTO ET AL) 2 July 1996 (1996-07-02)

D2: US-A-5 496 808 (BARGIOTTI ALBERTO ET AL) 5 March 1996 (1996-03-05)

D3: EDER JP ET AL: 'Sequence effect of irinotecan (CPT-11) and topoisomerase II inhibitors in vivo' CANCER CHEMOTHERAPY AND PHARMACOLOGY, DE, SPRINGER VERLAG, BERLIN, vol. 42, no. 4, 1998, pages 327-335,

2. The subject-matter of the present claims appears to be novel over the prior art, since products comprising the two required elements have not been disclosed before (Art 33(2) PCT).

3. The used anthracyclines are however known from D1 and D2 as antineoplastic agents. It is further suggested in D3 to combine antineoplastic agent with inhibitors of topoisomerase and that this combination would have a synergistic activity. For the skilled person it appears to be obvious to combine the teachings of D1 or D2 with D3 and arrive at the subject-matter of the present claims, i.e. the requirements of Article 33 (3) PCT have not been fulfilled.
It is pointed out that not even a synergistic effect can provide evidence for an inventive step, since this effect has been suggested in D3.

4. For the assessment of the present claims 7-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference FC 861/5	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/00745	International filing date (<i>day/month/year</i>) 31/01/2000	(Earliest) Priority Date (<i>day/month/year</i>) 25/02/1999
Applicant PHARMACIA & UPJOHN S.P.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the **international application** in the language in which it was filed, unless otherwise indicated under this item:

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/00745

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/396 A61K31/351 A61P35/00 A61K31/352
 //((A61K31/396, 31:352), (A61K31/396, 31:351), (A61K31/352, 31:351),
 (A61K31/351, 31:351))

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 48503 A (CARUSO MICHELE ;GERONI CRISTINA (IT); PHARMACIA & UPJOHN SPA (IT);) 30 September 1999 (1999-09-30) claims 1-7 ---	1-9
Y	EDER JP ET AL: "Sequence effect of irinotecan (CPT-11) and topoisomerase II inhibitors in vivo" CANCER CHEMOTHERAPY AND PHARMACOLOGY, DE, SPRINGER VERLAG, BERLIN, vol. 42, no. 4, 1998, pages 327-335, XP002112007 ISSN: 0344-5704 abstract page 334 --- -/-	1-9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 May 2000

Date of mailing of the international search report

22/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/00745

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 532 218 A (BARGIOTTI ALBERTO ET AL) 2 July 1996 (1996-07-02) cited in the application claims 1,6,10 ---	1-9
Y	US 5 496 808 A (BARGIOTTI ALBERTO ET AL) 5 March 1996 (1996-03-05) cited in the application claims 1,2,29 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/00745

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WU 9948503	A	30-09-1999	AU	3331499 A	18-10-1999
US 5532218	A	02-07-1996	AT	157369 T	15-09-1997
			AU	676625 B	13-03-1997
			AU	1066095 A	03-07-1995
			CA	2154890 A	22-06-1995
			CN	1117734 A, B	28-02-1996
			DE	69405214 D	02-10-1997
			DE	69405214 T	29-01-1998
			DK	683788 T	27-10-1997
			WO	9516695 A	22-06-1995
			EP	0683788 A	29-11-1995
			ES	2107294 T	16-11-1997
			FI	953784 A	09-08-1995
			GR	3025266 T	27-02-1998
			HU	73172 A	28-06-1996
			IL	111725 A	15-07-1998
			JP	8506835 T	23-07-1996
			NO	953163 A	02-10-1995
			NZ	276401 A	24-10-1997
			PL	310177 A	27-11-1995
			ZA	9409701 A	12-12-1995
US 5496808	A	05-03-1996	AT	134376 T	15-03-1996
			AU	661012 B	13-07-1995
			AU	2229492 A	11-02-1993
			CA	2112818 A	21-01-1993
			CN	1069981 A, B	17-03-1993
			CZ	9400024 A	13-07-1994
			DE	69208400 D	28-03-1996
			DE	69208400 T	27-06-1996
			DK	521458 T	18-03-1996
			WO	9301201 A	21-01-1993
			EP	0521458 A	07-01-1993
			FI	940011 A	03-01-1994
			GR	3019429 T	30-06-1996
			HK	1006460 A	26-02-1999
			HU	70480 A	30-10-1995
			IE	76921 B	05-11-1997
			IL	102409 A	08-12-1995
			JP	6508841 T	06-10-1994
			MX	9203928 A	01-04-1993
			NO	940026 A	16-02-1994
			NZ	243450 A	25-11-1993
			ZA	9204971 A	31-03-1993

PATENT COOPERATION TREATY

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REC'D 31 MAY 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference FC 861/5	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/00745	International filing date (day/month/year) 31/01/2000	Priority date (day/month/year) 25/02/1999
International Patent Classification (IPC) or national classification and IPC A61K31/396		
Applicant PHARMACIA & UPJOHN S.P.A.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 15/09/2000	Date of completion of this report 29.05.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrera, S Telephone No. +49 89 2399 8464



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/00745

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-6 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/00745

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-9
 No: Claims

Inventive step (IS) Yes: Claims
 No: Claims 1-9

Industrial applicability (IA) Yes: Claims 1-6
 No: Claims

2. Citations and explanations
see separate sheet

Section V

1. Reference is made to the following documents:
 - D1: US-A-5 532 218 (BARGIOTTI ALBERTO ET AL) 2 July 1996 (1996-07-02)
 - D2: US-A-5 496 808 (BARGIOTTI ALBERTO ET AL) 5 March 1996 (1996-03-05)
 - D3: EDER JP ET AL: 'Sequence effect of irinotecan (CPT-11) and topoisomerase II inhibitors in vivo' CANCER CHEMOTHERAPY AND PHARMACOLOGY, DE, SPRINGER VERLAG, BERLIN, vol. 42, no. 4, 1998, pages 327-335,
2. The subject-matter of the present claims appears to be novel over the prior art, since products comprising the two required elements have not been disclosed before (Art 33(2) PCT).
3. The used anthracyclines are however known from D1 and D2 as antineoplastic agents. It is further suggested in D3 to combine antineoplastic agent with inhibitors of topoisomerase and that this combination would have a synergistic activity. For the skilled person it appears to be obvious to combine the teachings of D1 or D2 with D3 and arrive at the subject-matter of the present claims, i.e. the requirements of Article 33 (3) PCT have not been fulfilled.
It is pointed out that not even a synergistic effect can provide evidence for an inventive step, since this effect has been suggested in D3.
4. For the assessment of the present claims 7-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

INTERNATIONAL SEARCH REPORT

Int'l. Jonal Application No
PCT/EP 00/00745

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/396 A61K31/351 A61P35/00 A61K31/352
//(A61K31/396, 31:352), (A61K31/396, 31:351), (A61K31/352, 31:351),
(A61K31/351, 31:351)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 48503 A (CARUSO MICHELE ;GERONI CRISTINA (IT); PHARMACIA & UPJOHN SPA (IT);) 30 September 1999 (1999-09-30) claims 1-7	1-9
Y	EDER JP ET AL: "Sequence effect of irinotecan (CPT-11) and topoisomerase II inhibitors in vivo" CANCER CHEMOTHERAPY AND PHARMACOLOGY, DE, SPRINGER VERLAG, BERLIN, vol. 42, no. 4, 1998, pages 327-335, XP002112007 ISSN: 0344-5704 abstract page 334	1-9

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

12 May 2000

22/05/2000

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INTERNATIONAL SEARCH REPORT

Int'l	Final Application No
PCT/EP 00/00745	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 532 218 A (BARGIOTTI ALBERTO ET AL) 2 July 1996 (1996-07-02) cited in the application claims 1,6,10	1-9
Y	US 5 496 808 A (BARGIOTTI ALBERTO ET AL) 5 March 1996 (1996-03-05) cited in the application claims 1,2,29	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Jonal Application No

PCT/EP 00/00745

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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			IE	76921 B		05-11-1997
			IL	102409 A		08-12-1995
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			MX	9203928 A		01-04-1993
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			ZA	9204971 A		31-03-1993